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IL-17 in the immunopathogenesis of spondyloarthritis

Leonie S. Taams[1*], Kathryn J.A. Steel[1], Ushani Srenathan[1], Lachrissa A. Burns[1] and Bruce W. Kirkham[2]

[1] Centre for Inflammation Biology and Cancer Immunology (CIBCI), Department of Inflammation Biology, School of Immunology & Microbial Sciences, King's College London, London, UK.

[2] Department of Rheumatology, Guy's and St Thomas' NHS Foundation Trust, London, UK.

*email: leonie.taams@kcl.ac.uk

Abstract

Spondyloarthritis (SpA) is a term referring to a group of inflammatory diseases that includes psoriatic arthritis, axial spondyloarthritis and nonradiographic axial spondyloarthritis, reactive arthritis, enteropathic arthritis and undifferentiated SpA. The disease subtypes share clinical and immunological features including the following: joint inflammation (peripheral and axial skeleton); skin, gut and eye manifestations; and the absence of diagnostic autoantibodies (seronegative). The diseases also share genetic factors. The aetiology of SpA is still the subject of research by many groups worldwide. Evidence from genetic, experimental and clinical studies has accumulated to indicate a clear role for the interleukin-17 (IL-17) pathway in the pathogenesis of SpA. The IL-17 family consists of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F, of which IL-17A is the most well-studied. IL-17A is a proinflammatory cytokine that also has capacity to promote angiogenesis and osteoclastogenesis. Of the six family members, IL-17A has the strongest homology with IL-17F. In this Review, we discuss how IL-17A and IL-17F and their cellular sources might contribute to the immunopathology of SpA.

Introduction

The IL-17 family consists of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F, of which IL-17A, commonly referred to as IL-17, is the best characterised member. IL-17A was identified in 1993 when it was referred to as cytotoxic T lymphocyte antigen-8 (CTLA-8) [1] (**Figure 1** and **Box 1**). As we discuss later in this Review, IL-17A was initially described as a product of CD4+ T cells (**Box 2**) but is now known to be produced by CD8+ T cells, γδ T cells, natural killer T (NKT) cells, mucosal-associated invariant T (MAIT) cells and a range of other immune cells. The expression of IL-17A is regulated by inflammatory cytokines. Specifically, the relationship between IL-23 and IL-17 has led to the concept of the IL-23/IL-

17 axis as a pivotal pathway contributing to host protection and inflammation (**Figure 1, Box 2**) [2,3].

IL-17A has been implicated in the immunopathology of several inflammatory diseases, including inflammatory arthritis (reviewed elsewhere [3,4]), and its effector function has been extensively studied. IL-17A signalling in IL-17 receptor-bearing target cells (**Box 3**) including fibroblasts, epithelial cells and synoviocytes results in the transcription of proinflammatory genes, leading to the secretion of a range of proinflammatory cytokines (including IL-6, TNF and IL-1) [5], T cell and myeloid-cell-attracting chemokines (CC-chemokine ligand 20 (CCL20), CCL2 and CCL7) [6,7] and neutrophilic granulocyte-attracting chemokines (CXC-chemokine ligand 1 (CXCL1), CXCL2, CXCL5 and CXCL8) [5,8]. Additionally, IL-17A enhances the production and secretion of granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage (GM)-CSF in stromal cells, macrophages and T cells, thereby enhancing granulopoiesis [9]. IL-17A also regulates production of antimicrobial peptides (defensins and S100 proteins) by IL-17 receptor-bearing target cells [10].

Although IL-17A has an important role in inflammation and host protection against specific pathogens, excessive activation of this pathway can contribute to autoimmunity or chronic inflammatory disease. In the context of inflammatory arthritis, IL-17A can induce the production of matrix metalloproteinases (MMPs) (matrix metalloproteinase 1 (MMP1), MMP9 and MMP13) from target cells, thereby driving the degradation of extracellular matrix within the joint [11,12]. Furthermore, IL-17A can upregulate receptor activator of nuclear factor-kB (NF-kB) ligand (RANKL; also known as TNFSF11) expression by osteoblasts, which can subsequently lead to osteoclast activation and bone destruction [13]. IL-17A also promotes

angiogenesis, thus increasing blood flow and facilitating the influx of inflammatory cells into the inflamed joint [14,15].

Several reports have shown that IL-17F functions in a similar manner to IL-17A, albeit with less potency; the literature describes a hierarchy in inflammatory potential with IL-17A homodimers eliciting the strongest inflammatory response, followed by IL-17AF heterodimers, and then IL-17F homodimers [16]. IL-17F has been shown to upregulate proinflammatory mediators including IL-6, CXCL1, CXCL8, GM-CSF, CCL2, CCL7 and MMP13 in fibroblasts and epithelial cells [17,18]. Furthermore, IL-17F has been linked to neutrophilia in the context of severe asthma[19].

These experimental data demonstrate the potent proinflammatory, osteoclastogenic and angiogenic capacity of IL-17A and/or IL-17F and suggest that these cytokines are critical drivers of inflammation. In this Review, we consider evidence from genetic studies, experimental models, in vitro experiments and clinical studies that implicate the IL-23/IL-17 axis and the cells that produce IL-17, in particular CD8+ T cells, in the immunopathogenesis of spondyloarthritis (SpA).

The evolving concept of spondyloarthritis

In 1859, Garrod distinguished immune-mediated inflammatory arthritis from gout and tuberculous arthritis [20,21]. Clinical pattern recognition remained paramount in identifying arthritis subtypes until the discovery of rheumatoid factor [22] provided a pathological basis for the division of seropositive and seronegative arthritis groups. Ankylosing spondylitis (AS), which primarily affects the spine, was recognised as a specific clinical entity in 1973, with reports of a strong relationship with HLA-B27 genotype confirming a different genetic basis

to rheumatoid arthritis (RA) [23,24]. Peripheral seronegative arthritis was less well defined until the recognition of overlapping clinical features occurring in people with the skin condition psoriasis; Moll and Wright thus coined the term psoriatic arthritis (PsA) in 1963 [25]. The ClASsification for Psoriatic ARthritis (CASPAR) criteria were subsequently developed in 2006 [26]. The overlapping clinical, immunological and genetic characteristics of the 'seronegative arthritides' led to the suggestion that these conditions could be considered a single entity called SpA, including axial spondyloarthritis (axSpA) (extending the former definition of AS to include those identified by nonradiographic means), PsA, enteropathic arthritis, reactive arthritis and undifferentiated SpA, with a combined population prevalence of 1-2% [27,28]. These conditions all have differing components of peripheral and axial (spine and sacro-iliac joint) arthritis, enthesitis, dactylitis, uveitis, inflammatory bowel disease (IBD), and psoriasis or psoriaform skin involvement [29]. The non-articular disease components, such as psoriasis or Crohn's disease, can be the dominant manifestation of these diseases. The broadening of the definition of SpA reflects increasing awareness of non-rheumatoid inflammatory arthritis as well as the impact of new imaging modalities.

Role of IL-17 family members in SpA

Although the mechanisms underlying SpA pathogenesis have not been completely elucidated, evidence suggests a clear role for the IL-23/IL-17 axis in this process. In the following section, we discuss the association of genetic variants in the major histocompatibility complex (MHC) class I pathway and the IL-23/IL-17 axis with susceptibility to SpA. We briefly review the role of IL-23/IL-17 in animal models of inflammatory arthritis, and discuss data regarding the presence of IL-17 family members in the blood and tissues of patients with SpA. Finally, we discuss how IL-17 could promote joint inflammation and disrupt bone

homeostasis by synergising with other proinflammatory cytokines.

Genetics of SpA with a focus on the MHC class I pathway and the IL-23/IL-17 axis

Although some evidence suggests the involvement of MHC class II in AS [30], the strongest association with genetic susceptibility to SpA lies within the MHC class I region. To date, the *HLA-B27* region represents the strongest genetic risk association identified in axSpA, PsA and reactive arthritis [31-33], and positivity for *HLA-B27* is strongly associated with sacroiliitis in both AS and PsA. In addition, multiple other variants within the MHC class I loci are associated with PsA (including *HLA-B39, HLA-Cw6*, *HLA-B38* and *HLA-B08*) or AS (*HLA-A02, HLA-B07*), with some associations most evident when patients are stratified by clinical characteristics [30,34-36]. The association of SpA with a variety of different HLA-B loci indicates that several immunological mechanisms could be altered by these genetic associations, including T cell repertoire selection and antigen presentation [37]. Given that MHC class I molecules present peptides to CD8+ T cells, this genetic association suggests that CD8+ T cells are implicated in SpA. Initially, variants in the *HLA-B27* region were thought to contribute to disease susceptibility through direct presentation of an arthritogenic peptide to cytotoxic CD8+ T cells [38]. Alternative data suggest that variants within this locus promote HLA-B27 homodimerization, instead of heterodimerization with β2 microglobulin [39] or that HLA-B27 protein misfolding occurs, activating the unfolded protein response and increasing IL-23 production [40,41]. Finally, HLA-B27 homodimers bind with increased affinity to killer cell immunoglobulin-like receptor 3DL2 (KIR3DL2), which is expressed on IL-17+ CD4+ T cells from the blood and synovial fluid of patients with AS [42]. These data suggest a link between MHC class I and the IL-23/IL-17 axis.

In addition to the HLA region, variants in the *ERAP1/2* loci (which encode enzymes required for HLA class I peptide trimming [43-45]), and the *RUNX3* locus, which encodes runt-related transcription factor 3, a transcription factor essential for CD8+ T cell development and differentiation [46-48], are associated with AS and PsA as well as psoriasis [49-52]. The location of susceptibility variants associated with PsA has been shown to overlap with epigenetic marks of transcription (histone H3 lysine 4 trimethylation (H3K4me3), a histone modification and epigenetic marker of active promoters) in memory CD8+ T cells [52]; in AS, susceptibility variants overlap with H3K4me3 marks across a range of immune cell types, including CD4+ and CD8+ T cells [53]. Furthermore, risk and protective variants in the *RUNX3* region correlate with variations in CD8+ T cell counts [49,54] and transcription factor (interferon regulatory factor 4, IRF4) binding [55], respectively. These genetic data provide a strong rationale to suggest the involvement of CD8+ T cells in SpA.

An additional pathway highlighted by genetic association studies in SpA is the IL-23/IL-17 axis. Variants in the *IL12B* region, which encodes the IL-12p40 subunit shared between IL-12 and IL-23, are associated with AS and PsA, as well as with psoriasis and IBD [49,50,56,57]; a variant in the *IL23A* region that encodes the IL-23p19 subunit is also associated with PsA and psoriasis [58]. Furthermore, susceptibility variants in the *IL23R* locus (which encodes IL-23 receptor) are associated with AS, PsA, psoriasis and IBD [45,49,56,57,59]. In patients with AS, susceptibility variants in the *IL23R* locus are associated with altered transcript levels of genes related to the T helper 1 (T_H1) and/or T_H17 cell response including *IL17A* and *RORC* [60]. These data suggest the involvement of IL-23 in the development of SpA. Interestingly, SpA and Behçet syndrome have several overlapping genetic associations (for example, variants in *IL23R*, *ERAP1* and HLA class I genes), indicating that these 'MHC-I-opathies' may have similar underlying immunopathology [61].

As IL-23 is known to be important for sustained IL-17 production, it is interesting that additional susceptibility variants associated with inflammatory diseases have been identified in genes encoding IL-23/IL-17-related signalling molecules including *TYK2*, *TRAF3IP2* and *STAT3*. Variants in the *TYK2* locus, encoding a tyrosine kinase required for IL-23 signalling, are associated with AS, PsA and IBD [52,56,59]. Variants in the *TRAF3IP2* (which encodes NFκB-activator 1 (ACT1; also known as TRAF3IP2) are associated with PsA, psoriasis and IBD [50,52,59]. ACT1 is a key ubiquitin ligase required for IL-17 signalling through the IL-17 receptor complex and subsequent induction of the NFκB pathway [62] (**Box 3**). Furthermore, genotyping studies have shown a suggestive association between *STAT3* and AS [63,64] and PsA [65]. Signal transducer and activator of transcription 3 (STAT3) is a transcription factor induced upon IL-23 (as well as IL-6 and IL-21) signalling in CD4+ T cells and is a main regulator of the differentiation and function of IL-17 producing CD4+ T cells [66,67].

Finally, studies have reported genetic associations with *TNFAIP3* (which encodes TNFα-induced protein 3) and/or *TNIP1* (which encodes TNFAIP3-interacting protein 1) in psoriasis [68], PsA [52] and IBD [59], with a suggestive association for AS [69]. TNFAIP3 is an anti-inflammatory, ubiquitin modifying enzyme that can dampen NFkB-mediated inflammation and that has been implicated in multiple autoimmune and inflammatory conditions; TNFAIP3 restrains IL-17 signalling in stromal cells [70]. TNIP1 is a critical factor controlling IL-17 biology in non-hematopoietic cells (keratinocytes and fibroblasts) both *in vivo* and *in vitro* [71]. **Figure 2** is a hypothetical depiction of how susceptibility genes associated with SpA might influence both CD8+ and CD4+ T-cell-related IL-23/IL-17-mediated immune responses.

IL-17 in animal models of SpA

A key role of IL-17 and IL-23 dependent pathways has been shown in many inflammatory arthritis models, including the early models said to represent RA, and those developed to model aspects of SpA. The adjuvant arthritis model, which uses arthritis-prone rat strains and the potent adjuvant Complete Freund's Adjuvant, is T-cell-dependent, lacks autoantibodies, and produces a resolving destructive inflammatory peripheral arthritis, osteitis and ankylosis of the tail [72]. The first demonstration that inhibiting IL-17A in an animal model reduced disease activity and joint damage was reported in this model [73]. Furthermore, collagen-induced arthritis (CIA), the archetypal model for RA, cannot be induced in IL-17 or IL-17R knockout animals [74-76]; development of arthritis in this model is dependent on IL-17 in the early phases, and partly suppressed by IL-17A inhibition during the active inflammatory phase. Conversely, overexpression of IL-17 with adenoviral vectors exacerbates CIA severity and joint destruction [77]. In the streptococcal cell wall model of inflammatory arthritis, prevention of IL-17 signalling blocks transition from transient arthritis to persistent arthritis after repeated inoculations [78].

A comprehensive review of animal models of pathogenic SpA pathways classified the models into related groups of HLA-B27 overexpression, TNF overexpression, IL-23 dependent models and curdlan-induced arthritis in SKG mice [79]. Studies of mechanisms of B27 overexpression in rats demonstrated expansion of IL-17+ CD4+ T cells [40,80], whereas a role for CD8+ T cells was not supported [81,82]. The SKG mouse, which has a tyrosine-protein kinase Zap70 T cell receptor defect, develops arthritis and autoantibodies in response to a natural fungal lung infection; this model was originally described as a model for RA [83]. However, specific pathogen-free mice injected with fungal derivatives develop different features, with downstream effects on SpA-associated genes. A detailed study of this model revealed many SpA features, including gut and skin inflammation and uveitis, followed by autoantibody formation [84]. IL-23 mediates the effects on local mucosal dysregulation and the

production of cytokines driving the SpA syndrome, including IL-17-dependent arthritis and IL-22-dependent enthesitis [85].

Enthesitis precedes joint inflammation in the CIA model [86], and the introduction of exogenous IL-23 by mini-circle DNA implants results in enhanced enthesitis. This process is mediated by IL-17 produced by IL-23R+ CD3+ CD4- CD8- lymphoid cells resident at the enthesis [87]. Finally, certain mouse strains spontaneously develop a dermatitis resembling psoriasis and joint ankylosis as they age, and important roles of IL-17 have been described in these models particularly in the early stages of the disease [88,89].

Presence of IL-17A and IL-17F cytokines in SpA

Several studies have reported increased IL-17 production or enhanced *IL17* mRNA expression in the serum, synovial fluid or tissue of patients with RA compared to patients with osteoarthritis (OA) and healthy individuals, indicating the presence of IL-17 in immune-mediated arthritis [13,15,90-94]. IL-17 has also been detected in the serum or synovial fluid of patients with early RA, suggesting its importance in disease initiation [94,95].

Compared with RA, fewer studies have focused on SpA; however, IL-17 and/or IL-23 levels are substantially higher in serum from patients with SpA (consisting of AS, reactive arthritis and/or undifferentiated SpA) than in age and sex-controlled healthy individuals [96,97]. In patients with AS, serum levels of IL-17 positively correlated with disease activity, as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [98,99]. Regarding the site of inflammation, higher levels of IL-17 have been detected in the synovial fluid than in the serum of patients with PsA [91], and in the synovial fluid of patients with reactive arthritis or undifferentiated SpA than in the synovial fluid of patients with OA or RA[100]. Furthermore, flow cytometry and western blot analysis revealed higher IL-17 receptor

A (IL-17RA) expression in synoviocytes from patients with PsA (and RA) than in OA synoviocytes [101]. An intestinal biopsy study described upregulation of *IL23A* (which encodes the p19 subunit) transcripts in the terminal ileum of patients with AS, suggesting that the gut is an important source of IL-23 in AS; however, upregulation of *IL17* mRNA was not observed in the same samples [102].

Data in the literature both support [103,104] and refute [105] the presence of IL-17F in RA, with few data available regarding the presence of IL-17F in SpA. Increased IL-17F expression, as measured by immunohistochemistry staining, was observed in synovial tissue from patients with PsA compared to OA synovial tissue [106], and *IL17F* mRNA expression was noted in 6 out of 14 synovial tissue samples from patients with PsA [107].

Synergistic effects of IL-17A and IL-17F

IL-17A can exert potent synergistic effects in the presence of other cytokines and mediators to augment proinflammatory responses, which could contribute to rheumatic disease. Although few studies have investigated the synergistic effects of IL-17A in the context of SpA, the literature on RA and experimental *in vitro* and *in vivo* systems is extensive, providing valuable insight into the synergistic function of IL-17A and its potential role in SpA (**Figure 3**).

One of the best-studied synergies is IL-17A with TNF. Reports show that IL-17A can synergise with TNF to induce increased production of proinflammatory mediators such as IL-6, IL-8 and CCL20 from RA synoviocytes [103,108,109]. The synergy between IL-17A and TNF enhances granulopoiesis by inducing increased levels of GM-CSF in RA synoviocytes [108] and G-CSF from human epithelial cells [110]. Moreover, IL-17A can combine with TNF to exhibit synergistic effects on the induction of CCL2 and CXCL2 from mouse mesangial cells [111]. In a

CIA mouse model, IL-17A and TNF overexpression in synovial tissue from knee joints results in increased joint inflammation and cartilage erosion; this process is associated with a synergistic increase in expression of S100A8 (an alarmin associated with cartilage destruction), IL-1β and MMPs[112]. Similarly, IL-17A and TNF synergistically increase levels of S100A8 in the antigen-induced arthritis mouse model [113] and increase MMP-2 and CXCR4 expression by RA synoviocytes, leading to an increase in cell invasion as examined by transwell Matrigel invasion chambers [114].

As previously mentioned, IL-17 can contribute to bone destruction by inducing production of RANKL and the induction of osteoclastogenesis. This destructive effect can be exacerbated in the presence of TNF. In the synovial membrane, mRNA levels of both *IL17A* and *TNF* are predictive of rapid joint damage progression in RA, particularly with shorter disease duration [115]. In an RA *ex vivo* bone explant model, the inhibitory effect of TNF blockade on collagen degradation was increased when combined with IL-17 and IL-1 blockade [116]. In addition, a study of TNF transgenic mice demonstrated that dual IL-17 and TNF blockade was more effective at restoring bone homeostasis than blockade of IL-17 or TNF alone; combined IL-17 and TNF inhibition led to decreased osteoclast and increased osteoblast numbers, increased osteocalcin levels and a reduction in RANKL levels, all contributing to protection from bone resorption [117].

Whereas systemic bone loss can occur in both RA and SpA, a characteristic feature of SpA is ectopic bone formation. The exact roles of inflammatory cytokines in new bone formation are still incompletely understood (reviewed elsewhere [118]). IL-17 can enhance the effects of TNF on bone matrix formation by mesenchymal stem cells (MSCs) [119]. These cytokines can synergistically enhance the mineralization of the MSC extracellular matrix, which is a marker

of human MSC differentiation into osteoblasts. Alkaline phosphatase (ALP), an enzyme produced by MSCs that is essential for bone mineralisation, is increased in the presence of IL-17 and TNF, whereas MSC RANKL expression is substantially downregulated [119]. However, further studies are required to determine the paradoxical effects of IL-17A and TNF on bone destruction and formation (**Figure 3**).

In addition to TNF, IL-17A has been shown to synergise with other proinflammatory cytokines including IL-1β and IFNγ. The combination of IL-17A and IL-1β increases IL-6 production by RA synoviocytes [120] and increases CCL20 production by fibroblast-like synoviocytes[121]. In the CIA mouse model, blocking both IL-17A and IL-1β reduces cartilage degradation and bone destruction and downregulates the expression of IL-1β, IL-6, IFNγ, RANKL and MMP-3 in cartilage tissue [122]. Moreover, a bispecific antibody for IL-17A and IL-1β improves clinical signs of CIA mice compared to blocking IL-17A or IL-1β alone [123]. IL-17A and IFNγ synergistically upregulate IL-6 and IL-8 production by keratinocytes and lead to a subtle increase in expression of intercellular adhesion molecule 1 (ICAM-1), a ligand that binds leukocyte adhesion glycoprotein LFA-1 α-chain (LFA-1A; also known as ITGAL) on T cells to cause T cell adhesion to keratinocytes [124]. This mechanism could augment inflammation in diseases of the skin, such as psoriasis.

Similar to IL-17A, IL-17F can synergise with other cytokines, amplifying its inflammatory potential. Real-time RT-PCR analysis revealed that IL-17F synergises with TNF to augment *IL6*, *IL8* and *CXCL5* mRNA levels from RA synoviocytes. Although the combination of IL-17A and TNF induces a higher fold increase in levels of mRNA for proinflammatory cytokines than IL-17F and TNF, the effect of IL-17F and TNF synergy is potent [103]. IL-17F can also synergise with TNF to induce elevated levels of G-CSF from human epithelial cells

[110] and synergises with both TNF and IL-1β, enhancing the expression of CCL2 and CXCL2 from mouse mesangial cells [111].

Although studies have demonstrated the proinflammatory capability of IL-17F, it remains to be firmly established that IL-17F contributes to the immunopathology of SpA; robust evidence confirming the presence and function of IL-17F in SpA is still lacking. However, if IL-17F is present, it has the potential to contribute to SpA pathology; reports suggest that IL-17F is not redundant to IL-17A and that dual blockade of these cytokines can further reduce inflammation compared with blockade of IL-17A alone. In a mouse model of colitis, combined blockade of IL-17A and IL-17F was more effective at ameliorating disease than blockade of IL-17A alone [125]. Moreover, dual neutralization of IL-17A and IL-17F might have a more profound effect on reducing T_H17 cell culture supernatant-induced IL-8 and IL-6 production by synoviocytes from patients with PsA and healthy human dermal fibroblasts than inhibition of IL-17A or IL-17F alone [107].

The mechanisms underlying the synergy of IL-17A and IL-17F with other cytokines remain to be fully elucidated; however, the synergistic effect might occur through the ability of IL-17A to stabilise mRNA transcripts. The IL-17A and TNF synergistic increase in IL-8 protein and gene expression has been shown to be the result of IL-17A extending the half-life of the unstable TNF-induced *IL8* mRNA (**Figure 3**) [126]. Given that cells pre-treated with a p38 mitogen-activated protein kinase (MAPK) inhibitor displayed an increased *IL8* mRNA decay rate after stimulation with IL-17A and TNF, IL-17A-induced mRNA stabilisation is proposed to be a p38 MAPK-dependent pathway [126]. The importance of ACT1 in IL-17A-induced stabilisation has also been highlighted [8], and other mRNA transcripts including *MIP2* and *CSF2* (which encodes GM-CSF) whose half-lives were extended in response to IL-17A have

been identified, implicating this as a common mechanism for IL-17A synergy. To date, no studies have investigated the ability of IL-17F to stabilise mRNA transcripts. The synergistic effect of IL-17A and TNF might also be mediated by phospholipase D enzymes, which upregulate cytokine secretion [127]; inhibition of these enzymes *in vitro* in RA fibroblasts that are cultured with IL-17A and TNF leads to decreased production of IL-6, IL-8 and CCL20 [127].

IL-17 producing T cells in SpA

Several cell types have been shown to produce IL-17, including T cells, innate lymphoid cells, NK cells, neutrophils and macrophages [4,128-130]. Here we focus on key T cell subsets that have been identified as sources of IL-17 in SpA.

IL-17A+ CD4+ T (T_H17) cells in SpA

The presence of CD4+ T cells expressing IL-17 (T_H17 cells, **Box 2**) in the inflamed rheumatoid joint has been documented extensively in patients with RA and juvenile idiopathic arthritis (JIA) [15,90,91,131-134], with evidence of correlations between the frequencies of these cells and disease activity or clinical phenotype [15,91,132]. In SpA, IL-17+ CD4+ T cells are present in higher frequencies in the peripheral blood of patients with PsA and AS than in healthy controls [135,136]. Furthermore, several studies have demonstrated the presence of IL-17+ CD4+ T cells in the synovial fluid of patients with PsA, AS or reactive arthritis [91,134,137,138]. As well as identifying increased IL-17+ CD4+ T cell frequencies in the peripheral blood of patients with psoriasis or PsA compared to healthy controls, increased frequencies of IL-17+ CD4+ T cells have also been identified in psoriatic lesional skin compared with skin from healthy individuals [139]. In patients with AS, frequencies of peripheral blood IL-17+ CD4+ T cells positively correlate with disease activity [99]. Correlations between IL-17+ CD4+

T cells percentages from the synovial fluid and levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, synovial fluid neutrophil count and synovial fluid total leukocyte count was also reported in a cohort of patients diagnosed with RA, SpA, undifferentiated SpA, reactive arthritis, microcrystal arthritis, gout and pseudogout [140].

IL-17+ CD8+ T cells in SpA

Evidence is increasing that CD8+ T cells are another cellular source of IL-17 (reviewed elsewhere [128]). An initial study reported *IL17* mRNA expression by human CD8+ T cell clones isolated from skin lesions of patients with psoriasis [124] (**Figure 1**). To date, the presence of IL-17+ CD8+ T cells has been shown in multiple immune-mediated inflammatory diseases such as psoriasis, multiple sclerosis and PsA[134,141-144]. An elegant study showed that IL-17+ CD8+ T cells are enriched in the epidermis of human psoriatic skin lesions, and that neutralizing anti-CD8 monoclonal antibody treatment of mice xenotransplanted with human psoriatic skin resulted in complete blockade of psoriasis development [145].

In SpA, IL-17+ CD8+ T cells are present in the peripheral blood of patients with AS, with the highest frequencies of these cells observed in patients with severe disease [146]. Furthermore, within the inflammatory joint, increased frequencies of IL-17+ CD8+ T cells are detected in the synovial fluid of patients with PsA or AS compared with peripheral blood from the same patients [134,138]. In PsA, this enrichment correlated with markers of disease activity such as the results of power Doppler ultrasonography and CRP levels [134]. Extensive immunophenotyping of IL-17+ CD8+ T cells from the synovial fluid of patients with SpA indicates that these cells have proinflammatory potential [147]. Notably, although frequencies of IL-17+ CD8+ T cells

are increased in the inflamed joints of patients with SpA, this enrichment has not been observed in the synovial fluid from patients with RA[134]. Thus, IL-17+ CD8+ T cells might specifically contribute to the pathogenesis of HLA class I-associated SpA, but not to HLA class II-associated RA.

T_{RM} cells in SpA

Tissue resident memory (T_{RM}) T cells are a subset of CD8+ or CD4+ T cells that do not re-circulate through the peripheral blood and lymphoid tissues [148,149]. Originally described in mice [150], T_{RM} cells are found in barrier tissues such as the lung, gut, skin, liver and genital tract [148,151,152], and have the potential to express IL-17A[152,153]. Characterised by expression of markers CD69 and/or CD103 (also known as ITGAE), T_{RM} cells are retained within tissue after activation, inducing a local inflammatory response through production of cytokines and cytotoxic mediators (reviewed elsewhere [154]). The transcription factor RUNX3 has been described as a key regulator of T_{RM} cell differentiation and homeostasis in mice [155]. Presently, very few human studies have described T_{RM} cells in patients with immune-mediated inflammatory diseases, although CD8+ T_{RM} cells have been described in both healthy and psoriatic skin, where T_{RM} cells express several cytokines including IFNy, IL-17A and IL-22 [144,152,156,157]. Less is known about CD4+ T_{RM} cells but they have been described in human skin [151]. Furthermore, IL-17A expressing T_{RM} cells were described as disease drivers in an experimental SpA mouse model [87]. In the context of inflammatory arthritis, few data have been published as yet, but these cells might be present in the synovial fluid of patients with JIA[158] and SpA [147]. Thus, this cell type might emerge as a relevant inflammatory cell type in the pathogenesis of inflammatory arthritis.

Mucosal-associated invariant T cells

MAIT cells are innate cells characterised by their variable region-α (Vα)7.2-joining region-α (Jα)33 rearrangement [159], high CD161 (also known as KLRB1) expression and MHC class I-related gene protein (MR1) restriction [160,161]. After stimulation with PMA (phorbol myristate acetate) and ionomycin, some MAIT cells produce IL-17, IFNγ, TNF or the cytolytic molecule granzyme B [162]. IL-17-producing CD8+ MAIT cells have been identified in psoriatic skin and blood from patients with psoriasis [163]; notably, frequencies of conventional Vα7.2- IL-17+ CD8+ T cells were higher than Vα7.2+ IL-17+ CD8+ (MAIT) T cells in the psoriatic skin.[162] We have previously identified low frequencies of IL-17-producing CD8+ CD161+ Vα7.2+ MAIT cells within the IL-17+ CD8+ T cell population in the synovial fluid of patients with PsA [134]. IL-17+ MAIT cells have also been identified at higher frequencies within the peripheral blood of patients with AS compared to the peripheral blood of healthy controls [164,165].

Invariant Natural Killer T cells

To date little evidence exists for the presence of IL-17-producing invariant NKT cells in SpA. One mouse study reported lower incidence and disease severity of induced arthritis in NKT-cell-deficient Jα281$^{-/-}$ mice than in B6 mice [166]. NKT cells were found to produce IL-17; Jα281$^{-/-}$ splenocytes produced little IL-17 compared to B6 splenocytes. In addition, a lower proportion of T_H17 cells was observed in Jα281$^{-/-}$ mice than in B6 mice, suggesting that NKT cells maintain or activate T_H17 cells, which can contribute to inflammatory disease.

γδ T cells

γδ T cells are a subset of T cells that combine typical features of adaptive T cells (antigen recognition via T cell receptors and pleiotropic effector functions) with an ability to

respond in a rapid, innate-like manner. These cells are present in the blood but predominantly reside in specific tissues. IL-17 expressing γδ T cells were initially described in patients with psoriasis, in whom the reduced percentage of variable domain-γ (Vγ)9Vδ2 T cells in the peripheral blood was attributed to an increase in cell trafficking to the inflamed skin [167]. Subsequently, the frequency of IL-17A expressing γδ T cells was reported to be increased in the peripheral blood of patients with PsA, AS, reactive arthritis and enthesis-related JIA compared with healthy controls [168-170]. IL-17A+ γδ T cells are also enriched in the synovial fluid compared with the peripheral blood of patients with PsA, reactive arthritis or undifferentiated SpA [170,171].

In mice, IL-23 responsive dermal γδ T cells secrete IL-17A, IL-17F and IL-22 and are implicated as key producers of IL-17A during psoriatic skin inflammation [172-174]. In a mouse model of SpA, retinoid-related orphan receptor-γ (RORC)+ IL-17A expressing γδ T cells accumulate in the enthesis, aortic root and eye, which are tissue sites commonly affected by SpA [175].

Other cellular sources of IL-17 in SpA

In addition to T cells, other non-T cell subsets have been identified as sources of IL-17. Increased levels of IL-17-producing group 3 innate-lymphoid cells (ILC3), a lineage negative cell population, have been identified in the peripheral blood of patients with PsA compared with healthy controls, the levels of which correlate with disease activity [176]. Increased levels of these cells have also been detected in the synovial fluid of patients with PsA compared with those with RA [177].

Other IL-17-producing cell types include CD3- CD56+ NK cells, which are found at higher levels in the peripheral blood of patients with enthesitis-related arthritis than in healthy controls [169]. Increased levels of IL-17-producing NK cells have also been identified in the synovial fluid in comparison to peripheral blood of patients with reactive arthritis or undifferentiated SpA [171]. Immunofluorescence microscopy on synovial tissue from patients with SpA showed co-localisation of tryptase-positive cells, identified as mast cells, and IL-17+ cells, suggesting the presence of IL-17-producing mast cells in SpA [178]. However, further studies demonstrated that mast cells do not synthesize IL-17, but rather capture, store and release bioactive exogenous IL-17A [179].

IL-23/IL-17 targeted therapies in SpA

Targeted therapies using cytokine specific monoclonal antibodies provide some of the most compelling evidence for the important roles of specific cytokine pathways in disease pathogenesis [180]. Studies investigating IL-23/IL-17-directed therapies have helped define the complexities of these pathways in SpA and related conditions such as psoriasis and IBD [181]. Ustekinumab, which targets the p40 subunit shared by both IL-12 and IL-23, was the first agent to show superior efficacy over TNF inhibitors in patients with psoriasis[182-184], albeit with less efficacy than TNF inhibitors in PsA [185,186]. High doses of this drug are also effective in Crohn's disease [187].

Anti-IL-17A directed therapies, initially secukinumab and then ixekizumab, have yielded outstanding responses in psoriasis, which have changed expectations of therapy; PASI90 (an improvement of 90% or more with respect to baseline Psoriasis Area and Severity Index score) and almost clear or clear responses occur in many patients, showing superiority to etanercept, adalimumab and ustekinumab [188-193]. Both secukinumab and ixekizumab have

shown efficacy in PsA. Secukinumab is also licensed for AS, with arthritis responses similar to those for TNF inhibitor therapy [194-199] but with no effect in uveitis [200]. In contrast to ustekinumab, IL-17 inhibition with secukinumab or ixekizumab is associated with low levels of exacerbation of IBD, demonstrating that IL-17A has a complex role [201]. Brodalumab, which is directed at IL-17RA and thereby blocks IL-17A, IL-17C, IL-17E and IL-17F signalling, has shown good efficacy in psoriasis and PsA [202-204], but causes exacerbation of Crohn's disease [205]. Bimekizumab, a bifunctional antibody that blocks both IL-17A and IL-17F, has demonstrated good efficacy in a proof-of-concept study in 39 patients with PsA [107], although randomised head-to-head studies are required to clarify whether dual IL-17A and IL-17F blockade is superior to IL-17A alone (as discussed above).

Specific inhibition of IL-23 by monoclonal antibodies targeting the IL-23p19 component has shown excellent efficacy in psoriasis, with response levels at least the same as for IL-17A inhibitors. Guselkumab, now licensed for psoriasis [206,207], has also shown efficacy in a phase II study of PsA [208,209]; tildrakizumab has demonstrated efficacy in a phase III study of psoriasis, and risankisumab has shown efficacy in phase II studies in psoriasis and Crohn's disease [210-212].

These clinical data help our understanding of the complex biological effects of IL-23/IL-17 pathways in SpA and related conditions. Data from skin and synovial tissue samples from patients with psoriasis and PsA, showing more extensive IL-17-related activation networks in skin versus synovial sites [213], might explain the difference in outcome of IL-17A inhibition in psoriasis versus PsA. Likewise, the differential responses of IL-23 versus IL-17A inhibition in Crohn's disease shows the complex role of IL-17A in the gut; furthermore, other effects of IL-23, such as IL-22 induction, might have an additive role.

Conclusions

The clinical, genetic and experimental evidence for a pathogenic role of IL-17A in SpA is compelling. In particular, the profound clinical efficacy of several drugs that target the IL-23/IL-17 pathway unequivocally demonstrates the contribution of this pathway in SpA. Importantly, IL-17A is not a sole contributor to SpA pathogenesis but acts in synergy with several other cytokines to drive the production of numerous other proinflammatory and tissue-modifying mediators. As is the case in other complex immune-mediated inflammatory diseases, SpA is probably the result of a combination of different factors culminating in imbalanced immune reactivity. The genetic evidence in SpA indicates the involvement of certain gene variants that might affect peptide presentation (MHC class I genes and *ERAP1/2*), alter CD8+ T cell development or differentiation (*RUNX3*), and/or promote increased IL-23 and/or IL-17 production (*IL23, IL23R, STAT3*) or IL-23/IL-17 signalling (*TYK2* and *TRAF3IP2*). Notably, targeted therapy using anti-cytokine monoclonal antibodies generally means that the targeted cytokine is inhibited regardless of the cellular source(s). The genetic and experimental evidence presented in this Review indicates that IL-17+ CD8+ T cells might be an important contributing source of IL-17A in SpA; however, these cells are not the only source of IL-17A. Whether IL-17 production by different cellular sources results in differential immunopathological effects remains to be established; these different effects could include, for example, differential cytokine co-expression leading to synergistic versus antagonistic effects, differences in migratory versus tissue-resident capacity by the IL-17 producing cell, co-existing cytotoxic potential, or as yet unknown factors. A detailed understanding of the cellular source(s) and molecular regulation of IL-17 in SpA might open up novel avenues to specifically intervene in the production of this cytokine, and thus help to ameliorate disease.

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Author contributions

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Key points

- Genetic and animal model studies indicate that the IL-23/IL-17 axis is involved in the pathogenesis of spondyloarthritis (SpA).
- IL-17A has been identified directly in the blood and synovial fluid of patients with SpA, with T cells representing a key source of this cytokine.
- IL-17A and IL-17F act in synergy with other proinflammatory mediators to induce proinflammatory responses across a range of cell types.
- IL-23/IL-17 targeted therapies have been shown to be effective in psoriatic arthritis and ankylosing spondylitis.

- Increased understanding of the pathogenic role of the IL-23/IL-17 axis, their cellular sources and molecular regulation in SpA is essential to develop novel therapeutic strategies targeting this pathway.

BOX 1. The IL-17 cytokine family

- IL-17A was first identified in 1993 through a subtractive hybridization screen of a rodent T cell library (then referred to as cytotoxic T lymphocyte antigen 8, CTLA8) [1] (**Figure 1**). Subsequent work detected *IL17A* mRNA in a human CD4+ T cell clone [5,214].
- Proteomic and genomic database searches led to the discovery of the remaining IL-17 family members, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F, all of which display a degree of similarity in amino acid sequences to IL-17A [215-217].
- Using nested RACE (rapid amplification of cDNA ends) PCR, IL-17F was first cloned, bearing the strongest (50%) homology to IL-17A. The *IL17F* gene was found to be located adjacent to *IL17A* on chromosome 6p12, and expression of IL-17F was observed in activated CD4+ T cells [217].
- Both IL-17A and IL-17F can be secreted as homodimers. In addition, mouse and human studies have identified an IL-17AF heterodimer [16,218].

BOX 2 T_H17 lineage discovery

- In 2005, two landmark studies defined IL-17A and IL-17F producing CD4+ T cells (T_H17 cells) as a distinct CD4+ T cell lineage separate from T_H1 and T_H2 cells [219,220] (**Figure 1**).

- T_H17 differentiation is dependent on signals from IL-6, transforming growth factor β (TGFβ), IL-1β and IL-21, whereas IL-23 is important for lineage maintenance [221-226]. IL-23 has also been shown to contribute to the pathogenicity of T_H17 subsets [219,227].
- The main regulator of T_H17 cells is the transcription factor retinoic acid related orphan nuclear receptor γ (RORγt) [228]. Other transcription factors that contribute to T_H17 differentiation include RORα, signal transducer and activator of transcription 3 (STAT3), interferon regulatory factor 4 (IRF4) and aryl hydrocarbon receptor (AHR) [66,229-232].
- In addition to IL-17A and IL-17F, T_H17 cells can produce an array of other cytokines including IFNγ, TNF, GM-CSF (granulocyte-macrophage colony-stimulating factor), IL-21, IL-22, IL-9 and IL-10. The presence and expression levels of these cytokines depend on the cytokine milieu present upon T_H17 polarisation [233-237], and they may synergise with or antagonise IL-17 function [233,235,236,238].

BOX 3 IL-17 Receptors and IL-17 Signalling

- The biological functions of IL-17 cytokines are mediated via surface receptors on target cells. There are five members of the IL-17 receptor family, IL-17 receptor A (IL-17RA), IL-17RB, IL-17RC, IL-17RD and IL-17RE.
- Functional IL-17 receptors exist as heterodimers, with IL-17RA as a common subunit. The IL-17RA and IL-17RC heterodimer is the receptor for IL-17A, IL-17F and IL-17A-IL-17F [239].
- IL-17RA is ubiquitously expressed at particularly high levels by hematopoietic cell types, whereas IL-17RC is preferentially expressed by non-hematopoietic cells [240].
- As IL-17A and IL-17F require IL-17RA and IL-17RC to exert their effects, these cytokines typically act on fibroblasts, epithelial cells and endothelial cells [240].

- Although the binding affinities of IL-17A and IL-17F for IL-17RC are comparable, research has shown a higher affinity of IL-17A for IL-17RA than IL-17F [218,241].
- A conserved region known as the similar expression of fibroblast growth factor genes and IL-17Rs (SEFIR) domain is located at the carboxy terminus of all IL-17 receptors. Upon IL-17 stimulation, the cytosolic protein nuclear factor-κB (NF-κB) activator 1 (ACT1; which is encoded by *TRAF3IP2*) is recruited to the IL-17 complex through homotypic interactions of the SEFIR domain [242,243].
- ACT1 serves as both a signalling adaptor, recruiting TNF receptor-associated factor 6 (TRAF6) proteins, and an E3 ligase, mediating the ubiquitination of TRAF6. This process leads to the activation of the canonical nuclear factor-κB (NFκB) pathway and mitogen-activated protein kinase (MAPK) pathways [242,243].
- A unique TRAF6-independent signalling pathway involves ACT1-dependent recruitment of TRAF2 and TRAF5, and this pathway mediates IL-17A-dependent mRNA stabilisation (reviewed elsewhere [242,243]).

LEGENDS

Figure 1. Key discoveries in the biology of IL-17A and IL-17-producing T cells. A timeline showing some of the major discoveries regarding IL-17A biology, IL-17 producing T cells and IL-17 targeted therapies is shown. AS, ankylosing spondylitis; CTLA8, cytotoxic T lymphocyte associated antigen 8; HVS13, Herpesvirus samiri; IL-23R, interleukin-23 receptor; PsA, psoriatic arthritis; RA, rheumatoid arthritis; T_{RM} cells, tissue resident memory cells.

Figure 2. Hypothetical depiction of how spondyloarthritis susceptibility genes might influence IL-23/IL-17-mediated immune responses.

RUNX3 variations might influence CD8+ T cell development or differentiation or the generation of tissue-resident memory (T_{RM}) cells. Gene variants in *ERAP1/2* might alter peptide trimming and thus major histocompatibility complex (MHC) class I-mediated peptide presentation to CD8+ T cells. MHC class I genotype can further influence peptide presentation to CD8+ T cells and/or lead to the formation of HLA-B27 homodimers. HLA-B27 homodimers can bind to killer cell immunoglobulin-like receptor 3DL2 (KIR3DL2), eading to IL-17 production by CD4+ T cells. Genetic variants in *IL12B*, *IL23A*, *IL23R* and *TYK2* might lead to enhanced IL-23 production and/or signalling, resulting in increased or sustained IL-17 production by CD8+ and CD4+ T cells. This increased IL-17 production might be exacerbated by genetic variations in *STAT3*, which signals downstream of IL-6, IL-21 and IL-23, all of which are important drivers of IL-17 production. Lastly, genetic variants in *TRAF3IP2* could lead to altered IL-17 signalling, while variants in *TNIP1* and/or *TNFAIP3* might influence nuclear factor-κB (NFκB) signalling. Together, these mechanisms could lead to enhanced IL-17 mediated biological effects (for example, production of IL-6, IL-8, CXCL1 and CCL20 in IL-17 receptor (IL-17R)-positive target cells. ER, endoplasmic reticulum; ERAP, ER aminopeptidase; IL-23R, IL-23 receptor; SpA, spondyloarthritis; TCR, T cell receptor.

Figure 3. Potential synergistic activity of IL-17A and TNF in the spondyloarthritis joint.

CD4+ and CD8+ T cells expressing IL-17A and TNF can act on target cells such as synovial fibroblasts in the inflamed spondyloarthritis joint. IL-17A can synergise with TNF, leading to increased production of proinflammatory mediators including IL-6, IL-8, CC-chemokine

ligand 20 (CCL20) and CXC-chemokine ligand 1 (CXCL1). Although the mechanisms of IL-17A and TNF synergy are not yet fully understood, it has been reported that IL-17A can extend the half-life of the unstable TNF-induced *IL8* mRNA via p38 mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NFκB) activator 1 (ACT1)-dependent pathways. The subsequent elevated levels of IL-8, IL-6 and CCL20 recruit neutrophils and lymphocytes, leading to an enhanced inflammatory response. The combination of IL-17A and TNF has also been reported to exacerbate disruption of bone homeostasis. These cytokines can augment the upregulation of receptor activator of NFκB ligand (RANKL) on osteoblasts and fibroblasts. Subsequently, osteoclast precursor cells expressing receptor activator of NFκB (RANK) are differentiated into activated osteoclasts that mediate bone degradation. Conversely, IL-17A and TNF can augment ectopic bone formation by increasing mesenchymal stem cell (MSC) differentiation into osteoblasts via mineralization of the MSC extracellular matrix. This process is associated with increased alkaline phosphatase (ALP) levels and decreased RANKL expression. Differentiated osteoblasts can then deposit new bone tissue. However, further studies are required to determine the paradoxical effects of IL-17A and TNF on bone destruction and formation. PsA, psoriatic arthritis; T_H17, T helper 17.

ToC

Evidence from genetic, experimental and clinical studies has accumulated to indicate a role for the interleukin-17 (IL-17) pathway in the pathogenesis of spondyloarthritis. This Review discusses how IL-17A and IL-17F and their cellular sources contribute to the immunopathology of these diseases.

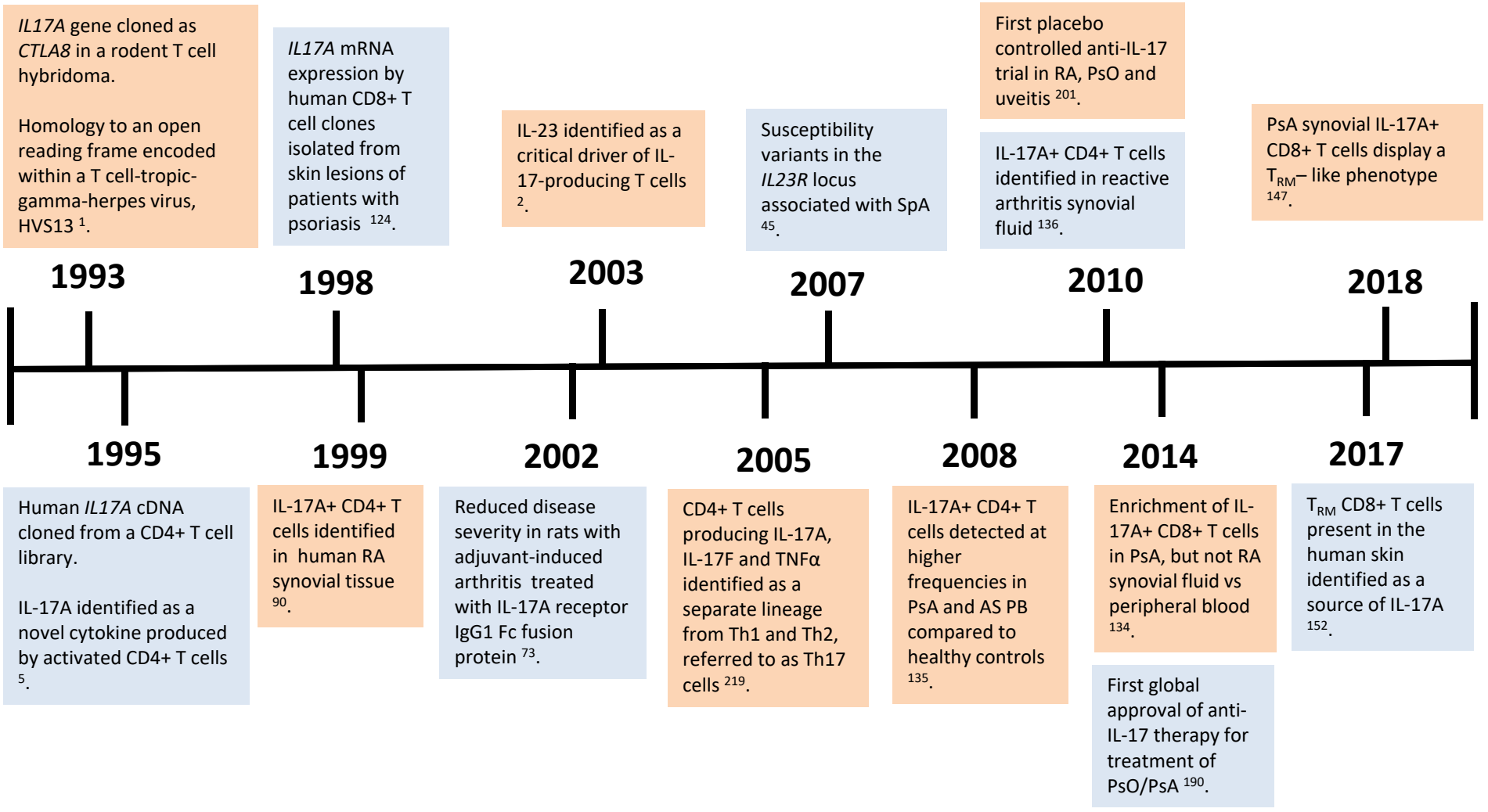

Figure 1. Taams et al.
Timeline of key discoveries in the biology of IL-17A and IL-17 producing T cells

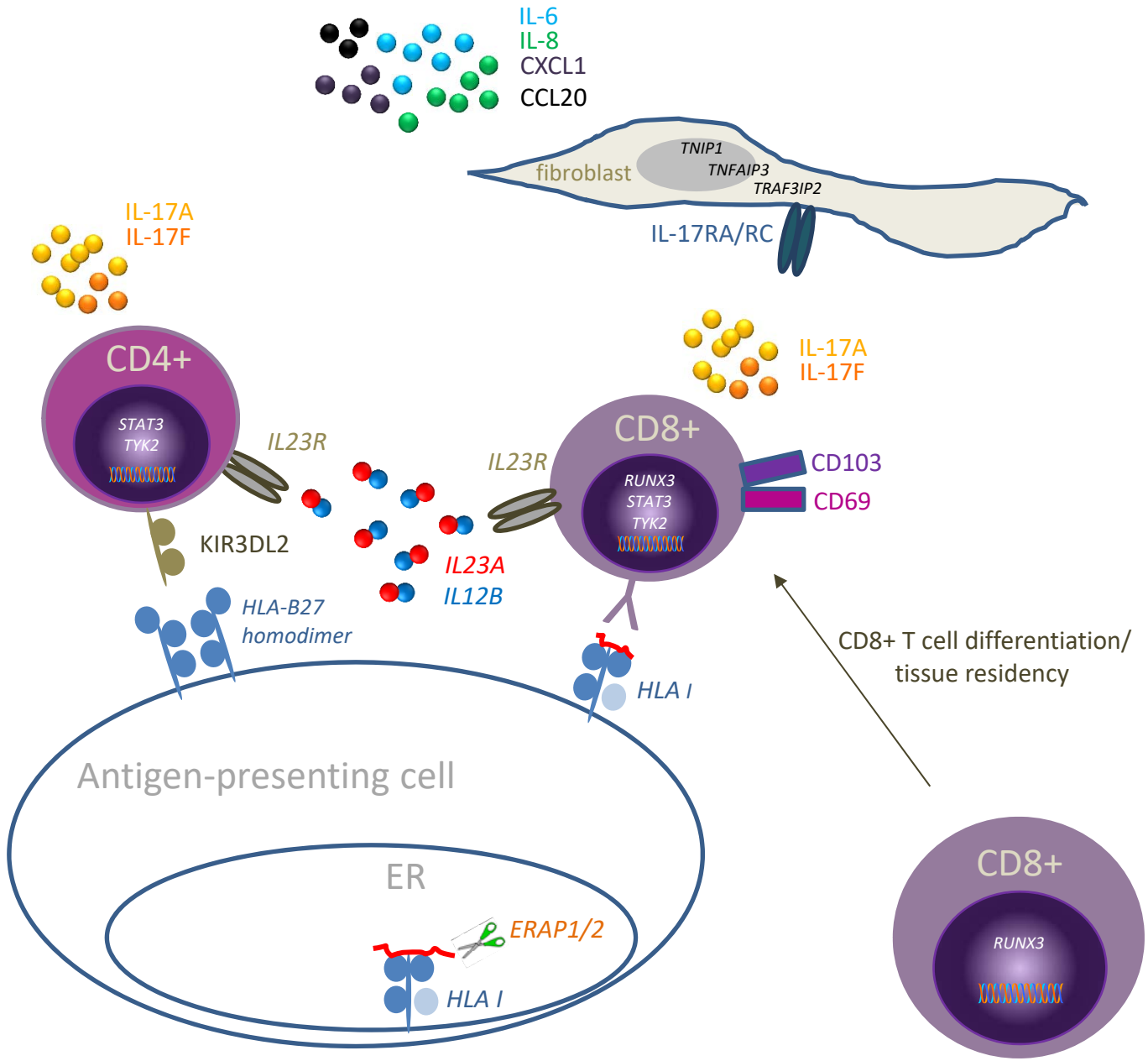

Figure 2. Taams et al.

Hypothetical depiction of how susceptibility genes associated with spondyloarthritis may influence IL-23/IL-17-mediated immune responses

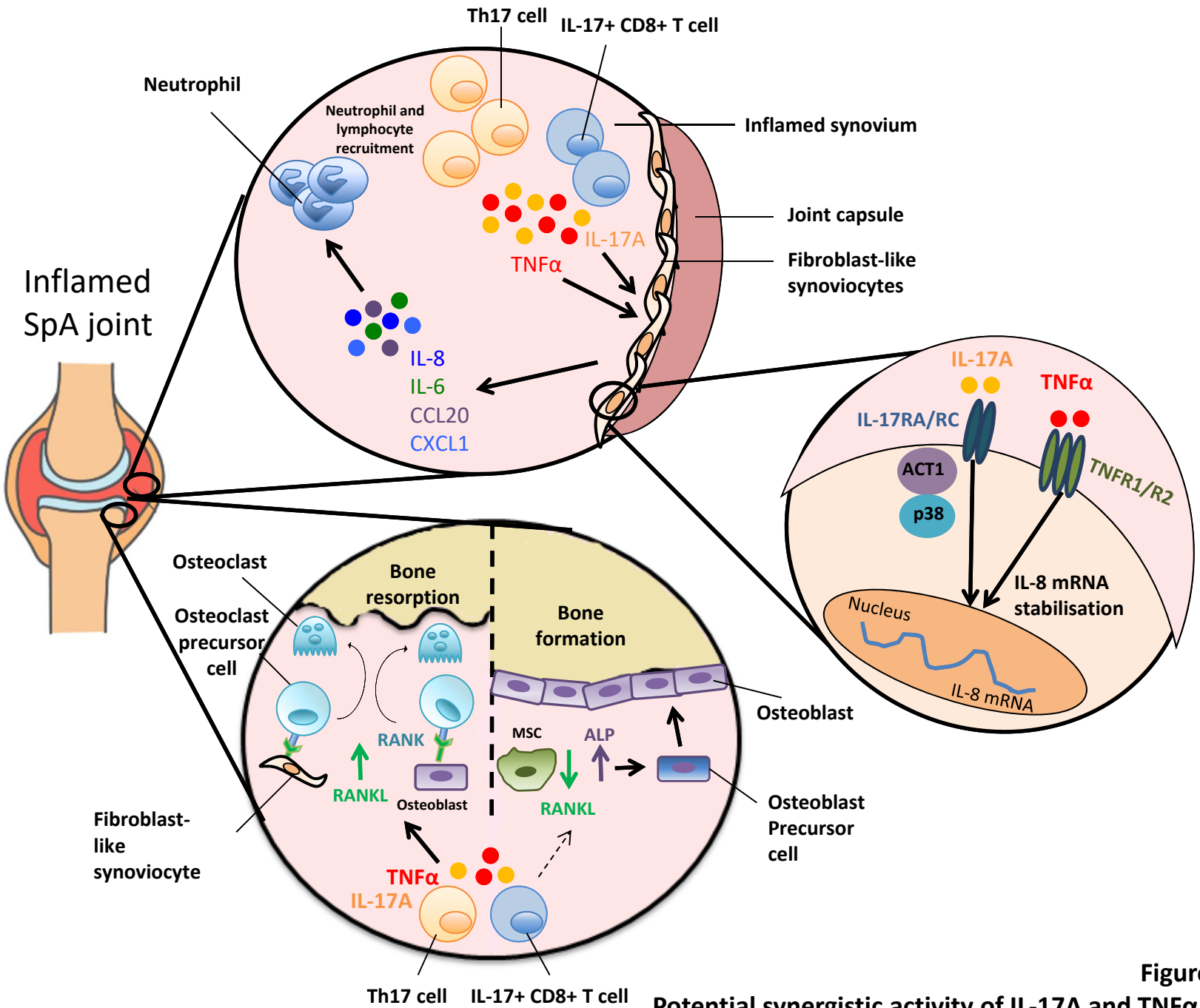

Figure 3. Taams et al.
Potential synergistic activity of IL-17A and TNFα in the SpA joint